~~30.~~ 29. A pharmaceutical preparation according to claim ~~8~~ 7 wherein said active ingredient is the compound 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-(2-methoxy)ethylester-5-propargyl ester.

~~31.~~ 30. A pharmaceutical preparation according to claim ~~8~~ 7 wherein said active ingredient is the compound 2,6-dimethyl-4-(2,3-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methylester-5-(2-methyl)allylester. End

In the Abstract of the disclosure

Page 41, line 16, between "$-CH_2CH_2OCH_3$," and "$-CH_2CH_2OC_2H_5$," insert --and--; and delete "and $(CH_2CH_2O)_2CH_3$".

Page 41, line 18, delete the compounds "$-CH(CH_3)C_2H_5$, $-CH_2CH_2OCH(CH_3)_2$,".

Page 41, line 19, delete the compound "$-CH_2C{=}CH$,".

Page 41, lines 20 and 21, delete "selected from the group consisting of".

Page 41, line 21, delete "and methoxy,".

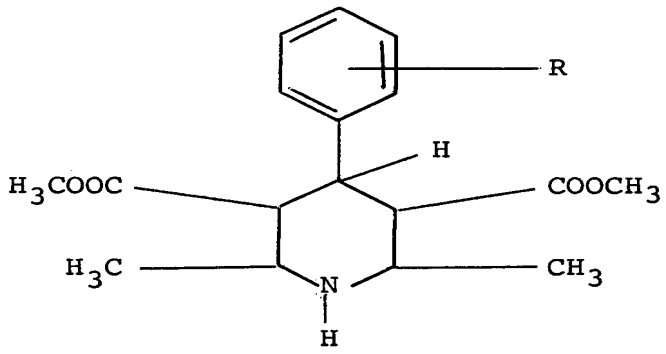
Page 41, line 22, between "chloro," and "methyl," insert --and--; and delete "and methoxy,".

R E M A R K S

Reconsideration of the rejection of this case is solicited in light of the above amendments and the following comments.

The claims added herewith present novel compound and pharmaceutical preparations in separate form, but dependent on parent claims 1 and 8. There is no new subject matter.

Compounds of the following formula:



wherein R is nitro or trifluoromethyl in the 2- or 3-position, are known to possess a cerebral vasodilating effect, an effect against angina pectoris, or a blood pressure lowering effect.

Agents which relax vascular smooth muscles have been used for the treatment of arterial hypertension since such patients suffer from elevated peripheral resistance to blood flow. Compounds which interfere with vascular smooth muscle activity have been used clinically for several years. However, their usefulness has often been limited due to insufficient efficacy and/or adverse side effects. Side-effects outside the cardiovascular system have often been connected with properties of the agents not relevant to the smooth muscle relaxing effect. Sometimes the vasodilating agents have also exerted a negative effect on the contractility of the heart.

It is apparent that the development of a specific smooth muscle relaxant, devoid of adverse side effects, would offer a therapeutic advantage in the treatment of arterial hypertension, ischaemic heart disease and the acutely failing heart. Furthermore, such agents would also be useful in treating other conditions arising from excessive activation of visceral smooth muscle.

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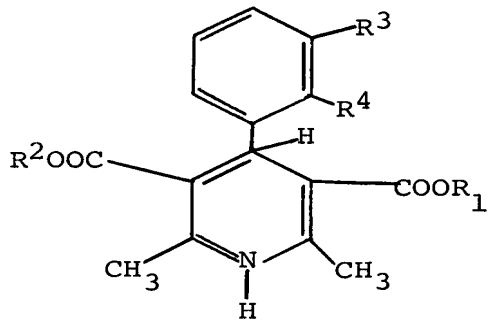
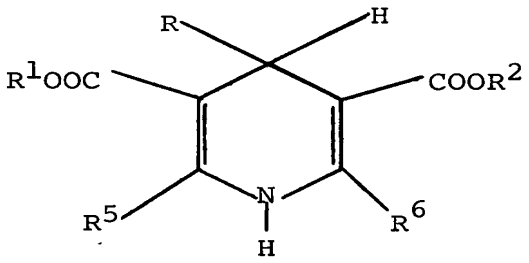
The compounds of the present invention are new antihypertensive agents, which lower blood pressure in the peripheral vessels in lower doses than they lower blood pressure in the heart vessels. The newly discovered compounds have the formula:



They have been shown by <u>in vitro</u> tests both to dilate peripheral blood vessels selectively relative to their effect on the heart muscle. The data set forth in the accompanying Declaration discussed more fully below demonstrate that the claimed compounds are significantly more selective in dilating peripheral blood vessels than are the compounds embraced by the prior art now relied on.

In the Official Action the Examiner states that claims 1-11 are rejected under 35 U.S.C. §103 as unpatentable over U.S. patent No. 3,799,936. The '936 patent relates to asymmetric esters of substituted phenyl-1,4-dihydropyridines of the following formula:



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wherein R is phenyl, optionally substituted with up to three substituents from the group alkyl, alkoxy, halogen, trifluoromethyl, and carboalkoxy, R^5 and R^6 are the same or different and are each hydrogen or alkyl, R^1 is alkenyl, alkynyl or alkoxyalkyl, and R^2 is different from R^1 and is alkenyl, alkynyl or alkoxyalkyl.

The Examiner now concedes that the '936 patent does not anticipate the present invention under 35 U.S.C. §102, but asserts nonetheless that the '936 patent makes the claimed subject matter obvious under 35 U.S.C. §103.

In a general manner the '936 patent shows the following:

1) a 1,4-dihydro-3,5-dicarboxylic-2,6-dimethyl pyridine nucleus

2) asymmetric-esterification of the carboxyl moieties

3) a phenyl ring at the four position of the pyridine nucleus

4) from 1-3 substitutes of various types in the phenyl ring.

While the Examiner points to each of these as being "indisputable" it is equally indisputable that the Meyer patent does not disclose the 2,3 substitution of the phenyl ring which is set out in the claims of this application. Indeed, it is evident from the disclosure of Meyer that he had no inkling of the 2,3 substitution which the present applicants have discovered. Of the 20 examples in the '936 patent, we find reference only to substitution such as 2-methoxy, 2-chloro, or 3,4-dimethoxy as having any bearing on the case.

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On the basis of a careful review of the 20 examples of the '936 patent the applicants believe that Example 14 of the '936 patent represents the compound most similar to the dichloro-substituted compounds of the present invention such as those illustrated in examples 2 and 6 of the application.* Example 14 of the '936 patent is an asymmetric ester having a 2-chloro substituent on the phenyl ring.

Tests of these compounds were carried out as described on the attached declaration of Dr. Berntsson, one of the inventors herein. Compounds tested were the following:

Compounds Tested

	R_1	R_2	R_3	R_4
2	$CH_2CH_2OCH_3$	C_2H_5	Cl	Cl
6	$CH_2CH_2OCH_3$	$CH(CH_3)$	Cl	Cl
A	C_2H_5	$CH_2CH_2OCH_5$	Cl	Cl

The claimed compound represented by Example 2 has a selectivity ratio of 78 and the claimed compound shown in Example 6 has a selectivity ratio of 107. Since the prior art compound A has a selectivity ratio of only 17, it is evident that this compound is less selective than the compounds of the present invention. The difference is substantial and unexpected.

*Referred to in Dr. Berntsson's Declaration as Examples 2 and 8, which were the example numbers prior to this amendment.

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In the Examiner's Official Action, he has referred to two additional compounds which he believes are relevant to the case. He cites specifically the compounds mentioned in Example 7 and in Column 4, namely, (a) 2,6-dimethyl-4-(2'-methoxymethyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-ethyl ester-5-β-propoxyethyl ester, and (b) 2,6-dimethyl-4-(2'-methoxymethyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-isopropyl ester-5-β-propargyl ester (hereafter "Compound C"). In view of the Examiner's comments, these two compounds have also been tested. The applicants point out that these compounds are most similar to the compound of Example 3 of the present specification, namely, 2,6-dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-methyl ester-5-isopropyl ester, as well as the compound of Example 6* of the present application, namely, 2,6-dimethyl-4-(2',3'-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid-3-β-methoxyethyl ester-5-isopropyl ester. Compounds in which R^3 or R^4 are methoxy have now been cancelled. The comparison of the compounds of these two examples with Compounds B and C shows the following:

TABLE II

Compound According to Example	SHR ED_{50} μ moles/kg bodyweight	Ratio heart vasc.
3	1	56
6	4	107
B	>125	61
C	24	79

*Originally, Example No. 8, and so referred to by Dr. Berntsson.

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From the foregoing summary of the data in Dr. Berntsson's Declaration, it is evident that the claimed compounds most closely similar to Compounds B and C cited by the Examiner are substantially and unexpectedly more active. It should be noted in this respect, as pointed out by Dr. Berntsson in his Declaration, that the claimed compounds have an ED_{20} potency which is in the general range of 1-15 µg/kg, together with high selectivity which combination makes the compounds claimed potentially anti-hypertensive drugs. Compounds with significantly lower activity (i.e., higher ED_{20} value), such as around ED_{20-25} or more, are generally not considered to be potentially useful as anti-hypertensive drugs. All three of the compounds of the reference patents which were tested exhibit an activity level which is significantly less than that believed to be substantially necessary for a clinically useful drug.

In light of the foregoing, we submit that the applicants have demonstrated that the compounds which are claimed in this case are unexpectedly superior to the prior art and, accordingly, favorable reconsideration of this application is solicited.

Respectfully submitted,

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